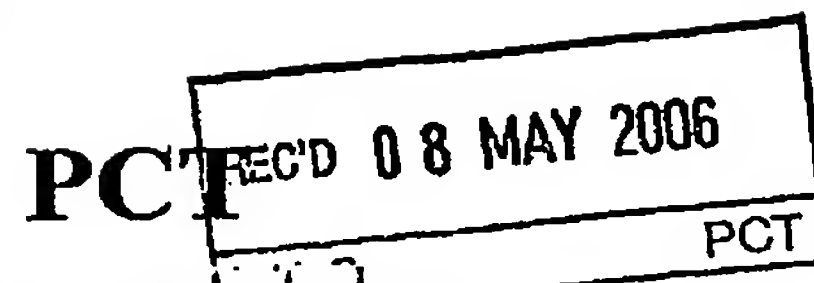


PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
G.E. EHRLICH
G.E. EHRLICH (1995) LTD.
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RAMTA GAN, ISRAEL 52 521



WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 28383		Date of mailing (day/month/year) 03 MAY 2006
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/IL04/01046	International filing date (day/month/year) 13 November 2004 (13.11.2004)	Priority date (day/month/year) 01 December 2003 (01.12.2003)
International Patent Classification (IPC) or both national classification and IPC IPC: Please See Continuation Sheet USPC: 435/325,352,354,363,366,383,391,392,455		
Applicant TECHNION RESEARCH & DEVELOPMENT FOUNDATION LTD.		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US Mail Stop PCT, Arm: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 30 March 2006 (30.03.2006)	Authorized officer Thaisan N. Ton <i>Thaisan N. Ton</i> Telephone No. 571-272-1600
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/IL04/01046

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
☐ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☒ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:
The priority claim is considered invalid because none of the claims are supported by the priority application.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 6

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 6 are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
no is CRF provided

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/IL04/01046

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-5 and 7-11

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL04/01046

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>3, 7-11</u>	YES
	Claims <u>1, 2, 4, 5</u>	NO
Inventive step (IS)	Claims <u>3</u>	YES
	Claims <u>1, 2, 4, 5, 7-11</u>	NO
Industrial applicability (IA)	Claims <u>1-5, 7-11</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-5 and 7-11 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Claims 1, 2, 4, 5 lack novelty under PCT Article 33(2) as being anticipated by Ratcliff et al. The claims are directed to isolated stem cells, particularly embryonic stem cells, wherein the stem cell carries a disease-carrying mutation, that is associated with a genetic disorder, such as cystic fibrosis. Ratcliff et al teach the disruption of the cystic fibrosis transmembrane conductance regulator gene in mouse embryonic stem cells.

Claims 1, 2, 4, 5 lack novelty under PCT Article 33(2) as being anticipated by Van Doorninck et al., because they teach production of mutated mouse ES cell line, particularly the delta-F508 mutation, associated with cystic fibrosis.

Claims 1, 2, 4, 5 lack novelty under PCT Article 33(2) as being anticipated by O'Neal et al, because they teach the production of mouse ES cells with a duplication in exon 3 in the cystic fibrosis locus.

Claim 3 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed invention.

Claims 7-11 lack an inventive step under PCT Article 33(3) as being obvious over Ratcliff et al or Van Doorninck et al or O'Neal et al when taken with Roach et al. Ratcliff, Van Doorninck and O'Neal all teach mutated mouse ES cell lines. They do not specifically teach the limitations in claims 7-11, with regard to the maintenance of the cells in an undifferentiated state, a normal karyotype, the pluripotent capacity of the cells, the culture medium of the cells. However, Roach et al. teach the critical components in maintaining mouse ES cells. They teach that in order to be considered ES cells, the cells must have a normal karyotype (p. 1, last paragraph), can continue to grow indefinitely in an undifferentiated diploid state (p. 1, 2nd paragraph). They teach media that can be used to maintain the cells, that includes fetal bovine serum (page 2, #2.3, Media and Reagents, #5). They teach the amount of FBS that is required in various media that the ES cells would grow in, which includes at least 10% FBS (Table 1, p. 3). Thus, the combined art provides the requisite teaching and motivation to arrive at the claimed invention, because Ratcliff, Van Doorninck and O'Neal provide a specific cell line, where Roach teach conditions in which to grow these cell lines. One of skill would reasonably expect these cell lines to be maintained under the conditions as taught by Roach.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 8 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: the term "isolated" is misspelled.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IL04/01046

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of IPC:

C12N 5/00(2006.01),5/02(2006.01),5/06(2006.01),5/10(2006.01),5/08(2006.01),15/63(2006.01)

C12N 15/85(2006.01),15/87(2006.01)